

# Current treatment strategies in locally advanced non-small cell lung cancer

## Review Article

H. Cuneyt Ulutin\* and Gorkem Aksu

Gulhane Military Faculty of Medicine, Radiation Oncology Department

\*Correspondence: Dr. Cuneyt Ulutin; Kizilcik sok. Kizilcikapt. 10/10 Anittepe Ankara Turkey; Telephone: 90-312-3044684; Fax: 90-312-3044150; e-mail: culutin@yahoo.com

**Key words:** locally advanced non-small cell lung cancer, chemotherapy, radiotherapy,

**Abbreviations:** American Society of Clinical Oncology, (ASCO); Cancer and Leukemia Group B, (CALGB); compared continuous hyperfractionated accelerated radiotherapy, (CHART); European Organization for Research and Treatment of Cancer, (EORTC); Non-Small Cell Lung Cancer, (NSCLC); radiotherapy, (RT)

Received: 30 November 2004; Revised: 6 December 2004

Accepted: 7 December 2004; electronically published: December 2004

## Summary

Lung cancer is the leading cause of cancer death in both men and women. By the time the patients seek medical attention, the disease is usually locally advanced or metastatic since symptoms of early-stage, localized disease is nonspecific. Complete surgical resection is possible in less than 30% of all lung cancers and the overall 5-year survival rate is less than 15%. 10–15% of lung cancer patients are stage IIIB at the time of initial diagnosis with a median survival of 8 months and a 5-year survival rate of < 5%. Surgery may be indicated in very selected patients for stage IIIB disease and the majority of patients are best managed with chemotherapy plus radiotherapy or with radiotherapy alone. In this review, we evaluated the current treatment strategies in locally advanced lung cancer by regarding the recent results of both phase III and phase II trials.

## I. Introduction

Lung cancer is the leading cause of cancer death in both men and women. In the United States alone, it was estimated that, approximately 170,000 new cases of lung cancer is seen per year and that lung cancer will account for 31% of cancer deaths in men and 25% cancer deaths in women, a total of nearly 160,000 deaths (Landis et al, 1999). Cigarette smoking is the main risk factor accounting for about 90% of the lung cancer deaths in men and about 85% in women. The other major occupational and environmental carcinogenic agents are arsenic, asbestosis, beryllium, chloromethyl ethers, chromicin, hydrocarbons, mustard gas, nickel and radiation (Saccomanno et al, 1976; US Department of Health & Human Services, 1988).

Symptoms of early-stage, localized disease is insidious and nonspecific, so by the time the patients seek medical attention, the disease is usually locally advanced or metastatic. Complete surgical resection is possible in less than 30% of all lung cancers and the overall 5-year survival rate is less than 15% (Ries et al, 1983).

Stage IIIA disease appears to be associated with a better prognosis than stage IIIB disease. According to the results of many studies, stage IIIA is associated with a

median survival time of 12 months and a 5-year survival rate of 15%, while stage IIIB disease is associated with survival time of 8 months and 5-year survival rate of < 5% (Ries et al, 1983; Mountain, 1997).

## II. Surgery in locally advanced lung cancer

Surgery may be indicated for stage IIIB disease only in carefully selected situations. Analyzing the patients who had T4N0–1 disease due to a satellite tumor nodule(s) within the primary tumor lobe it was seen that; such patients had a 5-year survival of approximately 20% with surgery alone (Deslauriers et al, 1989; Urschel et al, 1998). In a different study, 5-year survival of patients with T4N0–1 disease due to main carinal involvement who has been treated with carinal resection with or without pulmonary resection was approximately 20% (Darteville et al, 1988).

Neoadjuvant chemotherapy, or chemoradiotherapy followed by surgical resection, has been used in patients with N2 (IIIA) disease. A study by the Southwestern Oncology Group employed concurrent chemoradiotherapy in 51 patients with IIIB disease that excluded superior

vena cava syndrome and malignant effusions. The results of this study demonstrated a resectability rate of 80%, with a median survival time of 17 months and a 3-year survival rate of 24% (Albain et al, 1995). These results were similar for patients with IIIA disease reported in the same trial. However, up-to-date there is no phase III trial data that demonstrate, neoadjuvant treatment followed by surgery in patients with IIIB disease results in prolonged survival compared with combination chemoradiotherapy.

Still, there are no phase III trial data available to document that surgery adds to survival in patients with stage IIIB Non-Small Cell Lung Cancer (NSCLC) due to T4 (excluding Pancoast tumors) or N3 disease who are treated with neoadjuvant chemotherapy or chemoradiotherapy followed by surgery. The results of limited phase II trials are available so this approach should not be considered as standard therapy.

The role of surgery following induction chemotherapy or chemoradiotherapy for patients with initially unresectable cancer is being explored. In phase II testing, the use of concomitant chemoradiotherapy has led to improved resectability and overall survival compared with historical controls in patients with T3 to T4 NSCLC tumors of the superior sulcus (Rusch et al, 2001). The data from surgical series demonstrate that; induction chemotherapy does not result in increased risk of anastomotic complications in bronchoplastic or angioplastic surgical procedures (Roth et al, 1994, 1998; Rosell et al, 1999; Veronesi et al, 2002) but these findings shall be tested in randomized trials that will investigate the effect of induction chemoradiotherapy followed by surgical resection on survival.

Depending on sites of tumor involvement and performance score status, the majority of patients with IIIB disease does not benefit from surgery and are best managed with chemotherapy plus radiotherapy or with radiotherapy alone.

### **III. Induction chemotherapy**

The use of induction chemotherapy is based on several theoretic considerations. It has been suggested that the early use of the chemotherapy lowers the systemic tumor burden and prevents the growth of microscopic systemic disease, while bulky locoregional macroscopic disease is decreased and addressed more easily by surgery, radiotherapy or both. The role of induction chemotherapy combined with thoracic radiation has been investigated in patients with stage III NSCLC. The main advantage of induction chemotherapy is stage reduction to facilitate improved local control by radiation, surgery, or both. Micrometastases are addressed early in the course of treatment and the response rates to identical chemotherapy regimens appear to be higher when utilized for stage III disease than for stage IV disease. (Green, 1994). Finally, some studies suggest that induction chemotherapy is better tolerated than chemotherapy administered later in the course of treatment (Dillman et al, 1990, 1996; Sause et al, 1995).

CALGB 84-33 phase III trial in stage III NSCLC is one of the most important studies about induction chemotherapy (Dillman et al, 1990). Patients with

favorable performance status (Eastern Cooperative Oncology Group performance status, 0 or 1) and minimal weight loss (< 5% of body weight in the preceding 3 months) were randomized to receive 60 Gy of radiation in 6 weeks or two cycles of induction chemotherapy with cisplatin and vinblastine followed by identical RT.

An update of this trial has been published which included 7-year follow-up (Dillman et al, 1996). A total of 78 patients were randomized to chemoradiation, while 77 were randomized to RT alone. The objective response rate was 56% to combined treatment and 43% to RT alone ( $p = 0.092$ ). The group randomized to induction chemotherapy achieved a significant improvement in median survival compared to the group randomized to RT alone (13.7 vs 9.6 months, respectively;  $p = 0.012$ ) as well as improvement in the proportion of patients surviving 1, 2, 3, 5, and 7 years (54%, 26%, 24%, 17%, and 13% vs 40%, 13%, 10%, 6%, and 6%, respectively).

In The Radiation Therapy Oncology Group and Eastern Cooperative Oncology trial 452 eligible patients were randomized to the same two treatment arms employed in study CALGB 84-33 and a third arm that included hyper fractionation RT to a total dose of 69.6 Gy (Sause et al, 1995). The hyper fractionation RT arm had been demonstrated to produce a survival advantage for favorable patients in Radiation Therapy Oncology Group protocol 83-11 (Cox et al, 1990). Preliminary results of the confirmatory trial indicate that the 1-year survival rate and median survival time were superior in the group randomized to receive induction chemotherapy compared to the other two groups ( $p = 0.03$ ). The 1-year survival rate and median survival time for the three groups are as follows: induction chemotherapy and RT, 60% and 13.8 months, respectively; hyper fractionation RT, 51% and 12.3 months and standard RT, 46% and 11.4 months, respectively.

In the European Organization for Research and Treatment of Cancer (EORTC) trial which randomized 331 patients to three arms of 50-Gy thoracic RT in one arm and two other arms in which concurrent cisplatin and RT were utilized on one of two schedules (Schaake-Koning et al, 1992) Cisplatin was administered daily (6 mg/m<sup>2</sup>/d) along with radiation or weekly (30 mg/m<sup>2</sup>/wk). A significant survival advantage was obtained in daily cisplatin/radiation therapy arm compared with RT alone arm. 2- and 3-year survival rates were 26% and 16% vs. 13% and 2%, respectively ( $p = 0.009$ ). For weekly cisplatin and radiotherapy arm, 2- and 3-year survival rates were 19% and 13% with no significant difference from either of the other arms. Improved local control seems to be the cause of the survival benefit observed in daily cisplatin and radiotherapy group ( $p = 0.003$ ).

In a different multicenter study, 353 patients were randomized to receive 65-Gy radiation or to three cycles of induction chemotherapy with cisplatin, vindesine, cyclophosphamide, and lomustine given prior to RT followed by three additional cycles of chemotherapy (Le Chevalier et al, 1991, 1992). Although there was a very high rate of local-regional failure in both groups and local control was 17% in the RT arm and 15% in the combined-modality arm, the distant failure rate was significantly

reduced in the combined-modality arm compared to the RT arm (22% vs. 46% failure at 1 year, respectively;  $p < 0.001$ ). The response rate to induction chemotherapy was 27%. One-, 2-, and 3-year survival rates for the combined chemoradiotherapy arm were 50%, 21%, and 11%, respectively. The one-, 2- and 3 year survivals for the radiotherapy arm were 41%, 14%, and 5%, respectively ( $p = 0.08$ ). With a mean follow-up of 61 months, there was a statistically significant improvement in survival time associated with combined-modality treatment ( $p < 0.02$ ).

A meta-analysis of totally 2589 patients from 14 randomized trials comparing chemotherapy and RT to radiotherapy alone in regionally advanced stage III NSCLC revealed that the use of combination chemotherapy and RT reduces the risk of death by 12% at 1 year, 13% at 2 years, and 17% at 3 years (Pritchard and Anthony, 1996). This means a gain of life expectancy about 2 months. Similarly, the magnitude of benefit was independent of whether sequential or concurrent chemotherapy and RT were utilized.

Local-regional recurrence remains a major problem and most of the patients continue to have recurrences and metastatic disease, despite the use of chemoradiation for regionally advanced NSCLC. Green has emphasized that patterns of failure despite induction chemotherapy and RT mandate better control of both macroscopic intrathoracic disease and distant micrometastatic disease in the setting of regionally advanced NSCLC (Green, 1995).

In study CALGB 84-33, the group treated with chemoradiation had an 80% incidence of local-regional failure, while the group treated with RT alone had a 90% incidence of local-regional failure.

Phase II trials of induction chemotherapy and surgical resection in regionally advanced stage III NSCLC varied considerably with respect to many factors. The reasons of these variations are the usage of concomitant or sequential chemoradiotherapy in the studies, the differentiation in the choice and doses of chemotherapeutic agents, usage of different techniques in surgical staging of the mediastinum, different radiotherapy schedules, and also differences in the definition of resectable disease. Such inconsistencies have led to considerable difficulties in the interpretation of these trials (Skarin et al, 1989; Weiden and Piantadosi, 1991; Burkes et al, 1992; Reddy et al, 1992; Strauss et al, 1992; Martini et al, 1993; Elias et al, 1994, 1997; Jeremic et al, 1995; Sugarbaker et al, 1995; Choi et al, 1997).

Seven of these trials used preoperative RT (in six trials, RT was administered concurrently with chemotherapy, and in one trial it was administered sequentially), two trials used only postoperative RT, and two trials did not employ RT. Cisplatin-based combination chemotherapy regimens were used in all of the trials. Response rates to induction therapy varied from 39 to 77%. Resectability rates exceeded 50% in each of these trials. The highest resectability rate (93%) was noted in a trial that used hyperfractionated RT concurrently with induction chemotherapy (Choi et al, 1997) and the other trials reported pathologic complete response rates in the range of 10 to 20% following induction chemotherapy.

Analyzing the studies it was seen that, only a minority of patients had long-term survival and possible cure.

Two multi-institutional trials showed that patients who were found to have negative N2 lymph nodes at the time of resection had a significantly better survival rate than those with persistent N2 positive disease at resection (Albain et al, 1995; Sugarbaker et al, 1995).

Albain et al, (2003) reported the first outcome analysis of North American Intergroup trial 0139 (RTOG 93-09) which is a phase III study of concurrent chemotherapy and full course radiotherapy (CT/RT) versus CT/RT induction followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer. 392 patients were evaluated. All patients had induction with cisplatin 50 mg/m<sup>2</sup> d1,8 and etoposide 50 mg/m<sup>2</sup> and daily RT to 45 Gy starting day 1. Arm 1 underwent resection if no progression (PD) followed by two cycles of cisplatin and etoposide. Arm 2 received uninterrupted RT to 61 Gy and 2 cycles of cisplatin-etoposide. Induction chemoradiotherapy compliance was excellent (95%). Third and fourth cycles of cisplatin and etoposide were not received in 42% of patients in arm 1 and 21% of patients in arm 2 ( $p < 0.0001$ ). RT was per protocol in 97% of patients in arm 1 and 82% of patients in arm 2 ( $p = 0.002$ ). Most common grade 3/4 toxicities from chemoradiotherapy were neutropenia, emesis and esophagitis (9% in arm 1 and 20% in arm 2,  $p = 0.001$ ). Arm 1 had 14 deaths from treatment (6.9%), most of which were ARDS (postop, 4; during/after consolidation, 10). In Arm 2, 3 deaths (1.6%) occurred with/after consolidation. Patterns of failure were similar. The pathologic complete response rate was 36% in arm 1 and progression free survival was also superior in arm 1 (median, 14.0 vs 11.7 months; 3-year 29% vs 19%) ( $p = 0.02$ ). The median survival for each arm was 22 months (OS  $p = 0.51$ ). These first results showed that; the pathologic complete response rate in this trial was significantly higher than previous trials and chemoradiotherapy followed by surgery results in superior progression free survival. Final report is expected to determine if surgery significantly prolongs survival in stage IIIA(pN2) NSCLC (Albain et al, 2003).

None of these trials were designed to evaluate the therapeutic role of surgery in the context of regionally advanced disease, but the addition of surgery to the local-regional treatment regimen almost certainly accomplishes an improvement in local control. Local recurrence has generally been observed in < 50% of patients who undergo trimodality therapy. This contrasts with an 80 to 90% rate of persistent or recurrent local-regional disease among those patients who do not undergo resection. Thus, these phase II trials employing chemotherapy, RT, and surgery demonstrate a shift in recurrence patterns from both local and distant to predominantly distant. Furthermore, improved local control rates may result in significant gains in overall survival times as has been demonstrated in some other studies (Strauss et al, 1992; Jeremic et al, 1995).

Reports of small-randomized trials comparing induction chemotherapy followed by surgical resection to resection without systemic treatment have been influential in modifying the perception of the role of chemotherapy in the management of regionally advanced NSCLC.

A study from Spain, randomized patients to an induction chemotherapy regimen of cisplatin, mitomycin C, and ifosfamide followed by resection and postoperative RT (50 Gy) or to resection and the same postoperative RT. There was a dramatic threefold survival advantage for those patients randomized to receive induction chemotherapy (Rosell et al, 1994). In the group randomized to chemotherapy, the median survival time was 26 months, while in the group randomized to surgery plus radiotherapy, survival time was 8 months, which was lower than expected ( $p < 0.001$ ).

In a similar trial conducted at MD Anderson Cancer Center, patients were randomized to induction chemotherapy consisting of three cycles of cyclophosphamide, etoposide, and cisplatin followed by resection or to surgical resection alone (Roth et al, 1994). Of note, RT was given to  $> 50\%$  of patients in both arms of the study. There was a great difference in median survivals between two groups since while the group that received chemotherapy achieved an estimated median survival time of 64 months, the patients who were randomized to surgery alone had a median survival of 11 months ( $p < 0.008$ ). Similarly, the 3-year survival rate was 56% for the induction chemotherapy group compared with 15% for the surgery-alone group.

In randomized trial from the National Cancer Institute; the experimental group was treated with induction cisplatin and etoposide chemotherapy followed by resection and postoperative chemotherapy. The control group underwent immediate surgical resection and postoperative RT (54 to 60 Gy). Patients treated with induction chemotherapy had a superior survival time, but the difference was not statistically significant (28.7 vs. 15.6 months, respectively) (Pass et al, 1992).

Preliminary results of CALGB 9314 TRIAL which used induction chemotherapy with cisplatin and etoposide for two cycles followed by resection in one arm, two additional cycles of chemotherapy, and subsequent RT (54 or 60 Gy) in the second arm and a control arm of preoperative RT (40 Gy) followed by resection and postoperative RT (to a total dose of 54 or 60 Gy), show that the median overall survival time was 19 months for the group undergoing induction chemotherapy compared with 23 months for the group receiving preoperative RT (Elias et al, 1997).

Although three of these four randomized trials showed a survival benefit with the use of induction chemotherapy (including two trials in which the differences were statistically significant), these studies have significant limitations such as having small number of patients (totally 204 patients), early stoppings and possible imbalance of prognostic factors between the arms (Pass et al, 1992; Roth et al, 1994).

Despite the limitations of the randomized induction chemotherapy and surgery trials in stage IIIA NSCLC, the results of these trials lend some support to the conclusion that for favorable patients with stage IIIA NSCLC, induction chemotherapy followed by resection (with or without radiotherapy (RT)) may enhance disease outcome compared with that achieved with resection (with or without RT). While the magnitude of the survival

advantages added by chemotherapy are very likely to have been exaggerated, particularly in the MD Anderson Cancer Center trial, numerous phase II trimodality studies support a similar conclusion, though with a modest degree of effectiveness. In addition, these results for induction chemotherapy with surgery are consistent with numerous phase III studies that have demonstrated that induction chemotherapy with definitive RT improves outcome when compared with thoracic RT alone.

The recent results of both phase III and phase II trials provide a basis for optimism that real therapeutic progress is finally being achieved in regionally advanced NSCLC. Further study of therapeutic strategies that incorporate aggressive systemic treatment and maximal local-regional therapy in stage III NSCLC is clearly warranted.

In a prospective trial by Radiation Therapy Oncology Group (RTOG), ECOG, and the Southwest Oncology Group (SWOG), patients were randomized to receive 2 months of cisplatin + vinblastine chemotherapy followed by 60 Gy of radiation at 2 Gy per fraction; or 1.2 Gy / fraction radiation twice daily to a total dose of 69.6 Gy, or 2 Gy / fraction of radiation once daily to 60 Gy. Overall survival was statistically superior for the patients receiving chemotherapy and radiation versus the other two arms of the study (13.2 months  $\nu$  12 months,  $\nu$  11.4 months, respectively;  $p = 0.04$ ) (Sause et al, 2000). But; the survival benefit in this trial was less than that seen in the original Cancer and Leukemia Group B (CALGB) trial (Dillman et al, 1996). Distant metastasis was less for patients who received chemotherapy (Komaki et al, 1997). In a review of chemotherapy in NSCLC patients there was also a survival benefit in favour of chemotherapy (Non-small Cell Lung Cancer Collaborative Group Anonymous, 2000).

#### **IV. Concurrent and sequential chemoradiotherapy**

Administration of chemotherapy concurrently with radiation therapy theoretically improves local control by sensitizing the tumor to radiation, while simultaneously treating systemic disease, albeit at the expense of greater local toxicity. Two large phase III studies suggest improvement in both local control and survival with concurrent chemoradiotherapy as compared with sequential chemotherapy followed by radiation for patients with stage III NSCLC.

According to Furuse et al, (1999) randomized patients received either concurrent or sequential chemoradiotherapy. The concurrent arm demonstrated statistically significant superiority in response rate (84%  $\nu$  66%,  $P = .0002$ ) and median survival time 16.5  $\nu$  13.3,  $P = .040$ ). But myelosuppression was greater in the concurrent arm (Furuse et al, 1999).

In RTOG 94-10 trial which randomized patients to three arms: sequential cisplatin + vinblastine followed by thoracic radiation of 60 Gy; concurrent cisplatin + vinblastine with radiation to a total dose of 60 Gy; or cisplatin + etoposide concurrent with radiation to a total dose of 69.6 Gy delivered in twice-a-day fractions., median survival was superior in the concomitant

chemotherapy plus daily radiation arm compared with the sequential arm (17 months v 14.6 months;  $P = 0.08$ ). The concomitant chemotherapy plus twice-daily radiation arm demonstrated intermediate survival compared with the other study arms. Nonhematologic toxicity was also higher on the concurrent arms (Curran et al, 2000).

A French cooperative group performed a phase III randomized trial of sequential versus concurrent chemoradiotherapy in unresectable IIIA/IIIB patients. The chemotherapy was cisplatin and vinorelbine for 3 cycles, followed by thoracic radiotherapy (66 Gy/33 Fx), or concurrent cisplatin/etoposide, with thoracic radiotherapy followed by cisplatin and vinorelbine. Seventy-five percent of patients had IIIB disease, and over 100 patients were enrolled in each arm. Incidence of grade 3/4 esophagitis was 26% in patients in the concurrent therapy arm vs 0% in the sequential arm. The median survival time was 13.8 months with sequential therapy and 15 months with concurrent therapy. The 2-year survival rates were 23% and 35%, respectively. While there was a trend in favor of concurrent therapy, it was not statistically significant at the time of this preliminary report (Pierre et al, 2001).

These studies suggest improvement in both local control and survival with concurrent chemoradiotherapy as compared with sequential chemotherapy followed by radiation for patients with stage III NSCLC.

Therefore, based on these large phase III randomized trials, concurrent chemoradiotherapy appears to result in better survival than sequential therapy. It is associated with some increased toxicity, mainly acute esophagitis, and should be reserved for patients with PS 0 or 1 and minimal weight loss.

## V. Different radiotherapy schedules and fractionation

Different radiotherapy schedules and doses are used in some of the trials instead of conventional radiotherapy. In order to reduce long-term normal tissue toxicity by smaller fraction size and to reduce repopulation in rapidly proliferating tumors accelerated radiotherapy schedules are used. Accelerated radiotherapy is defined as the use of two or more fractions of standard fraction size daily to the same conventional total dose as standard radiotherapy, but increasing the number of fractions per week and shortening the overall treatment time. Hyperfractionated accelerated radiotherapy combines the features of accelerated and hyperfractionated regimen. It uses two or three fractions of smaller fraction size daily, delivered over a shorter period of time than conventional therapy.

A phase III trial compared continuous hyperfractionated accelerated radiotherapy (CHART) to standard radiotherapy (60 Gy/30 Fx). CHART consisted of three treatments per day (1.5 Gy/Fx), at least 6 h apart, for 12 days without a break (54 Gy). Sixty-one percent of patients were IIIA or IIIB. The 1- and 2-year survival rates for the CHART arm were 63% and 29%, respectively, vs 55% and 20% for standard radiotherapy. Overall, there was a 22% reduction in the relative risk of death ( $p = 0.008$ ). Acute esophagitis was more severe for patients

receiving CHART, but the incidence at 3 months was similar to patients receiving standard radiotherapy, and there was no difference in late morbidity. Recently, a phase III trial of HART (same as CHART except for no treatments on weekends) versus standard radiotherapy after induction chemotherapy had to be closed due to poor accrual in the Eastern Cooperative Oncology Group (Saunders et al, 1997, 1999).

Accordingly, at this time we have one phase III trial of CHART that showed superior survival over standard radiotherapy, but it had only 61% of patients with stage IIIA and IIIB disease, and no data are available concerning the combination of CHART and chemotherapy. Additionally, the schedule of radiotherapy 3 times per day seems to have been rejected by radiotherapists in North America. Therefore, at this time, neither CHART nor HART can be recommended as standard therapy. Optional dose, volume, and fractionation schedules are evolving. An RTOG randomized phase III trial in the 1980s demonstrated that 60 Gy produced a nonstatistically significant survival improvement compared with 50 Gy or two different schedules of 40 Gy (Perez et al, 1980). Accordingly, the dose of 60 Gy in 6 weeks has been widely used for 20 years. However, this dose and fractionation schedule results in local control rates of 15 to 30% (Perez et al, 1980; Le Chevalier et al, 1992; Saunders et al, 1997, 1999; Stuschke and Thames, 1997; Sause et al, 2000; Stella et al, 2001; Cancer Care Ontario Practice Guideline Initiative, 2002). Therefore, higher doses may yield better results. Guidelines of the American Society of Clinical Oncology (ASCO), (2004) advise that definitive dose thoracic radiotherapy should be at least 60 Gy in 1.8 to 2.0 Gy fractions.

For stage IIIB NSCLC patients, there is no convincing data that hyperfractionated (two or more fractions daily) radiotherapy is superior to standard once daily treatment. Two randomized prospective phase III trials (RTOG 9410 and NCCTG 94-24-52) compared chemotherapy plus either QD RT vs. BID RT. Neither found a survival advantage to BID RT. (Schild, curan). Continuous hyperfractionated accelerated radiotherapy (CHART) was demonstrated in one small trial to be superior to standard once daily therapy. Although incompleting, the findings of the ECOG trial and some other trials which evaluated hyperfractionated radiotherapy and chemotherapy were quite provocative and more investigation of TID fractionation is warranted (Oral et al, 1999; Kirkbride et al, 2002; Schild et al, 2002; Belani et al, 2003).

With the use of 3-D-Conformal radiotherapy it is now possible to give higher doses to the tumor volume than standard RT doses. In a recent study from Memorial Sloan-Kettering Cancer Center, seventy-two patients with Stage III NSCLC and gross tumor volumes (GTV) of greater than 100 cc were treated with three-dimensional conformal radiotherapy (3D-CRT). Patients were divided into two groups: those treated to less than 64 Gy (37 patients) and those treated to 64 Gy or higher (35 patients). The 1-year and 2-year local failure rates were 27% and 47% for patients who received 64 Gy or higher, and 61% and 76% for those treated to less than 64 Gy ( $p = 0.024$ ).

The median survival time for patients treated to 64 Gy or higher was 20 months vs. 15 months for those treated to less than 64 Gy ( $p = 0.068$ ). Multivariate analysis revealed that dose and GTV are predictors of local failure-free survival. A 10 Gy increase in dose resulted in a 36.4% decreased risk of local failure (Rengan et al, 2004).

Rosenmann et al. reported the reesults of a phase I/II clinical trial in which 62 Stage IIIA/IIIB inoperable non-small-cell lung cancer (NSCLC) patients were treated with two cycles of induction carboplatin/paclitaxel chemotherapy, followed by concurrent weekly carboplatin/paclitaxel with radiation doses escalated from 60 to 74 Gy. 48 patients completed the entire course of treatment. Eight patients (13%) suffered locoregional relapse as the only site of failure. Only 1 patient had Grade 2 radiation pneumonitis. Five patients (8%) had RTOG Grade 3 or 4 esophagitis; 40 (65%) had a Grade 1 or 2 esophagitis. The median survival was 24 months. The survival rate was 50% at 2 years and 38% at 3 years. The results showed that doses of 74 Gy appear to be safe and may possibly contribute to increased survival in patients with inoperable Stage IIIA/IIIB NSCLC (Rosenman et al, 2002).

Evaluating the results of these and some other studies it is suggested that administration of higher doses using 3D-CRT improves local control in Stage III NSCLC patients.

## VI. Duration of chemotherapy

The optimal duration of chemotherapy for patients with unresectable stage III NSCLC being treated with combined-modality therapy is still unclear and since no benefit was seen in studies when chemotherapy was continued until progression of disease, the duration of initial chemotherapy is recommended to be between two and four cycles of platinum-based therapy, with an upper limit of four cycles in the Guidelines of the ASCO (2004).

## VII. Gefitinib in locally advanced lung cancer

The use of epidermal growth factor receptor tyrosine kinase inhibitor, gefitinib in patients with advanced NSCLC with disease progression or intolerance to cisplatin or carboplatin and docetaxel is investigated in two phase II trials (Kris et al, 2002; Fukuoka et al, 2003). Two hundred ten patients with advanced NSCLC who were previously treated with one or two chemotherapy regimens (at least one containing platinum) were randomized to receive either 250-mg or 500-mg oral doses of gefitinib once daily. Efficacy was similar for the 250- and 500-mg/day groups. Objective tumor response rates were 18.4 and 19.0%. Symptom improvement rates were 40.3% and 37.0%, median progression-free survival times were 2.7 and 2.8 months and median overall survival times were 7.6 and 8.0 months, respectively. Adverse events at both dose levels were generally mild (grade 1 or 2) and consisted mainly of skin reactions and diarrhea. Drug-related toxicities were more frequent in the higher-dose group. The results showed that; Gefitinib showed clinically meaningful antitumor activity and provided

symptom relief as second- and third-line treatment in these patients. Having a favorable adverse effect profile at 250 mg/day, Gefitinib is recommended for the treatment of patients with locally advanced or metastatic non-small-cell lung cancer after failure of both platinum-based and docetaxel chemotherapies in the guidelines of ASCO (2004).

## VIII. Conclusion

As a result for stage IIIB NSCLC patients with PS 0 or 1 and minimal weight loss, concurrent chemoradiotherapy is still recommended as the standard therapy since randomized studies show that concurrent therapy appears to be associated with improved survival vs. sequential therapy. When radiotherapy is combined with chemotherapy, there is no convincing data that hyperfractionated (two or more fractions daily) radiotherapy is superior to standard once daily treatment.

Although further study of therapeutic strategies that incorporate aggressive systemic treatment and maximal local-regional therapy in stage III NSCLC is clearly warranted; by regarding the recent results of both phase III and phase II trials it can be hopefully declared that real therapeutic progress is about to be achieved in locally advanced NSCLC.

## References

- Albain KS, Rusch VW, Crowley JJ et al (1995) Concurrent cisplatin/etoposide plus chest radiation therapy followed by surgery for stage IIIA (N2) and IIIB non-small cell lung cancer, mature results of Southwest Oncology Group Phase II study 8805. *J Clin Oncol* 13, 1880-1892.
- Albain KS, Scott CB, Rusch VR, et al (2003) Phase III study of concurrent chemotherapy and full course radiotherapy (CT/RT) versus CT/RT induction followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): First outcome analysis of North American Intergroup trial 0139 (RTOG 93-09) *Lung Cancer* 41,Supplement 2, 4.
- American Society of Clinical Oncology (2004) Treatment of Unresectable Non-Small-Cell Lung Cancer, Guideline, Update 2003. *J Clin Oncol* 22, 2, 330-353.
- Belani CP, Wang W, Johnson DH et al (2003) Induction chemotherapy followed by standard thoracic radiotherapy (Std.TRT) vs. hyperfractionated accelerated radiotherapy (HART) for patients with unresectable stage III A & B non-small cell lung cancer (NSCLC): Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597). *Proc Am Soc Clin Oncol* 22, 622.
- Burkes RL, Ginsberg RJ, Sheperd FA et al (1992) Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage III unresectable non-small cell lung cancer, results of a Toronto phase II trial. *J Clin Oncol* 10, 580-586.
- Cancer Care Ontario Practice Guideline Initiative (2002) Altered fractionation of radical radiation therapy in the management of unresectable non-small cell lung cancer. (GPG 7-12)
- Choi NC, Carey RW, Daly W et al (1997) Potential impact on survival of improved tumor downstaging and resection rate by preoperative twice-daily radiation and concurrent chemotherapy in stage IIIA non-small cell lung cancer. *J Clin Oncol* 15, 712-722.
- Cox JD, Azarnia N, Byhardt RW et al (1990) A randomized phase I-II trial of hyperfractionated radiation therapy with

- total doses of 60.0 Gy to 79.2 Gy, possible survival benefit with > 69.6 Gy in favorable patients with radiation therapy oncology group stage III non-small cell lung carcinoma, report of radiation therapy oncology group 83-11 **J Clin Oncol** 8, 1543-1555.
- Curran WJ Jr, Scott C, Langer C et al (2000) Phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III non-small cell lung cancer (NSCLC), Initial report of radiation therapy oncology group (RTOG) 9410. **Proc Am Soc Clin Oncol** 19, 484.
- Darteville PG, Khalife J, Chapelier A et al (1988) Tracheal sleeve pneumonectomy for bronchogenic carcinoma, a report of 55 cases. **Ann Thorac Surg** 46, 68-72.
- Deslauriers J, Brisson J, Cartier R et al (1989) Carcinoma of the lung, evaluation of satellite nodules as a factor influencing prognosis after resection. **Thorac Cardiovasc Surg** 97, 504 - 512.
- Dillman RO, Herndon J, Seagren SL et al (1996) Improved survival in stage III non-small cell lung cancer, seven-year follow-up of Cancer and Leukemia Group B (CALGB) 8433 trial. **J Natl Cancer Inst** 88, 1210-1215.
- Dillman RO, Herndon J, Seagren SL et al (1996), Improved survival in stage III non-small-cell lung cancer, Seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. **J Natl Cancer Inst** 88, 1210-1215.
- Dillman RO, Seagren S, Propert K et al (1990) A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small cell lung cancer. **N Engl J Med** 323, 940-945.
- Elias AD, Herndon J, Kumar P et al (1997) A phase III comparison of "best local-regional therapy" with or without chemotherapy for stage IIIA T1-3N2 non-small cell lung cancer (NSCLC), preliminary results. **Proc Am Soc Clin Oncol Annu Meet** 16, 448a.
- Elias AD, Skarin AT, Gonin P et al (1994) Neoadjuvant treatment of stage IIIA non-small cell lung cancer, long-term results. **Am J Clin Oncol** 17, 26-36.
- Elias AD, Skarin AT, Leong T et al (1997) Neoadjuvant therapy for surgically staged IIIA N2 non-small cell lung cancer (NSCLC). **Lung Cancer** 17, 147-161.
- Fukuoka M, Yano S, Giaccone G, et al (2003) Multi-institutional randomized phase II trial of gefitinib for previously treated patients with advanced non-small cell lung cancer. **J Clin Oncol** 21, 2237-46.
- Furuse K, Fukuoka M, Kawahara M et al (1999) Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. **J Clin Oncol** 17, 2692-2699.
- Green MR (1994) Multimodality therapy for solid tumors. **N Engl J Med** 330, 206-207.
- Green MR (1995) Multimodality therapy in unresected stage III non-small cell lung cancer, the American Cooperative Groups' experience. **Lung Cancer** 12 (suppl 1), 87-94.
- Jeremic B, Shibamoto Y, Acimovic L et al (1995) Randomized trial of hyperfractionated radiation therapy with or without concurrent chemotherapy for stage III non-small cell lung cancer. **J Clin Oncol** 13, 452-458.
- Kirkbride P, Hatton M, Lorigan P et al (2002) Fatal Pulmonary Fibrosis Associated with Induction Chemotherapy with Carboplatin and Vinorelbine Followed by CHART Radiotherapy for Locally Advanced Non-small Cell Lung Cancer. **Clinical Oncology** 14, 361-366.
- Komaki R, Scott CB, Sause WT et al (1997), Induction cisplatin/vinblastine and irradiation vs. irradiation in unresectable squamous cell lung cancer, Failure patterns by cell type in RTOG 88-08/ECOG 4588\_Radiation Therapy Oncology Group Eastern Cooperative Oncology Group. **Int J Radiat Oncol Biol Phys** 39, 537-544.
- Kris MG, Natale RB, Herbst RS, et al (2002) A phase II trial of ZD1839 ('Iressa') in advanced non-small cell lung cancer (NSCLC) patients who had failed platinum- and docetaxel-based regimens (IDEAL 2). **Proc Am Soc Clin Oncol**, 21, 292a.
- Landis SH, Murray T, Bolden S, Wingo PA (1999) Cancer statistics 1999. **CA Cancer J Clin** 49, 8-31.
- Le Chevalier T, Arriagada R, Quoiz E et al (1991) Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer, first analysis of a randomized trial in 353 patients. **J Natl Cancer Inst** 83, 417-423.
- Le Chevalier T, Arriagada R, Tarayre M et al (1992) Correspondence-significant effect of adjuvant chemotherapy on survival in locally advanced non-small cell lung carcinoma [letter]. **J Natl Cancer Inst** 84, 58.
- Martini N, Kris M, Fhelinger B et al (1993) Preoperative chemotherapy for stage IIIA (N2) lung cancer, the Sloan-Kettering experience with 136 patients. **Ann Thorac Surg** 55, 1365-1374.
- Mountain CF (1997) Revisions in the International System for Staging Lung Cancer. **Chest** 111, 1710 -1717.
- Non-small Cell Lung Cancer Collaborative Group Anonymous (2000) Chemotherapy for non-small cell lung cancer. **Cochrane Database of Systematic Reviews** CD002139.
- Oral EN, Bavbek S, Kizir A, et al (1999) Preliminary Analysis of a Phase II Study of Paclitaxel and Continuous Hyperfractionated Accelerated Radiotherapy in Locally Advanced Non-Small Cell Lung Cancer. **Lung Cancer** 25, 191-198.
- Pass HI, Pogrebnick HW, Steinberg SM et al (1992) Randomized trial of neoadjuvant therapy for lung cancer, interim analysis. **Ann Thorac Surg** 53, 992-998.
- Perez CA, Stanley K, Rubin P et al (1980) A prospective randomized study of various irradiation doses and fractionation schedules in the treatment of inoperable non-oat cell carcinoma of the lung. **Cancer** 45, 2744-2753.
- Pierre F, Maurice P, Gilles R et al (2001) A randomized phase III trial of sequential chemoradiotherapy in locally advanced non-small cell lung cancer. **Proc Amer Soc Clin Oncol** 20, 312a.
- Pritchard RS, Anthony SP (1996) Chemotherapy plus radiotherapy compared with radiotherapy alone in the treatment of locally advanced, unresectable, non-small cell lung cancer. **Ann Intern Med** 125, 723-729.
- Reddy S, Lee MS, Bonomi P et al (1992) Combined modality therapy for stage III non-small cell lung cancer, results of treatment and patterns of failure. **Int J Radiat Oncol Biol Phys** 24, 17-32.
- Rengan R, Rosenzweig KE, Venkatraman E et al (2004) Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. **Int J Radiat Oncol Biol Phys** 60, 741-7.
- Ries LG, Pollack ES, Young JL (1983) Cancer patient survival, Surveillance, Epidemiology and End results program. **J Natl Cancer Inst** 70, 693 -709.
- Rosell R, Gomez-Codina J, Camps C et al (1994) A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small cell lung cancer. **N Engl J Med** 330, 153-158.
- Rosell R, Gomez-Codina J, Camps C, et al (1999) Pre-resectional chemotherapy in stage IIIA non-small-cell lung cancer, A 7-year assessment of a randomized controlled trial. **Lung Cancer** 26, 7-14.
- Rosenman JG, Halle JS, Socinski MA et al (2002) High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-

- small-cell lung cancer: technical issues and results of a phase I/II trial. **Int J Radiat Oncol Biol Phys** 54, 348-56.
- Roth JA, Atkinson EN, Fossella F, et al (1998) Long-term follow-up of patients enrolled in a randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. **Lung Cancer** 21, 1-6.
- Roth JA, Fossella F, Komaki R et al (1994) A randomized trial comparing preoperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small cell lung cancer. **J Natl Cancer Inst** 86, 673-680.
- Rusch VW, Giroux DJ, Kraut MJ, et al (2001) Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus, Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). **J Thorac Cardiovasc Surg** 121, 472-483.
- Saccomanno G, Archer VE, Saunders RP et al (1976) Early indices of cancer risk among uranium miners with reference to modifying factors. **Ann NY Acad Sci** 271, 377-383.
- Saunders M, Dische S, Barrett A et al (1997) Continuous hyperfractionated accelerated radiotherapy (CHART) vs conventional radiotherapy in non-small cell lung cancer, a randomized multicentre trial. **Lancet** 350, 161-165.
- Saunders M, Dische S, Barrett A et al (1999) Continuous, hyperfractionated, accelerated radiotherapy (CHART) vs conventional radiotherapy in non-small cell lung cancer, mature data from the randomized multicentre trial. **Radiation Oncol** 52, 137-148.
- Sause W, Kolesar P, Taylor S IV et al (2000) Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer. **Chest** 117, 358-364.
- Sause W, Kolesar P, Taylor SI et al (2000), Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer, Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. **Chest** 117, 358-364.
- Sause W, Scott C, Taylor S et al (1995) Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588, preliminary results of a phase III trial in regionally advanced, unresectable non-small cell lung cancer. **J Natl Cancer Inst** 87, 198-205.
- Schaake-Koning C, Van Den Bogaert W, Dalesio O et al (1992) Effects of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer. **N Engl J Med** 326, 524-530.
- Schild SE, Stella PJ, Geyer SM et al (2002) Phase III trial comparing chemotherapy plus once-daily or twice-daily radiotherapy in Stage III non-small-cell lung cancer. **Int J Radiat Oncol Biol Phys** 5, 370-8.
- Schild SE, Wong WW, Vora SV et al (2002) Phase I study of hyperfractionated accelerated radiotherapy and escalating doses of daily cisplatin for patients with locally advanced non-small-cell lung cancer. **Int J Radiat Oncol Biol Phys** 54, 729-734.
- Skarin A, Jochelson M, Sheldon T et al (1989) Neoadjuvant chemotherapy in marginally resectable stage III M0 non-small cell lung cancer, long-term follow-up in 41 patients. **J Surg Oncol** 40, 266-274.
- Stella P, Marks R, Schild S et al (2001) Phase III trial of chemotherapy either standard radiotherapy or accelerated hyperfractionated thoracic radiotherapy for stage III non-small cell lung cancer. **Proc Amer Soc Clin Oncol** 20, 312a (1245).
- Strauss GM, Herndon JE, Sherman DD et al (1992) Neoadjuvant chemotherapy and radiotherapy followed by surgery in stage IIIA non-small cell carcinoma of the lung, report of a Cancer and Leukemia Group B phase II study. **J Clin Oncol** 10, 1237-1244.
- Stuschke M, Thames HD (1997) Hyperfractionated radiotherapy of human tumors, overview of the randomized clinical trials. **Int J Radiat Oncol Biol Phys** 37, 259-267.
- Sugarbaker DJ, Herndon J, Kohman, LJ et al (1995) Results of Cancer and Leukemia Group B Protocol 8935, a multiinstitutional phase II trimodality trial for stage IIIA (N2) non-small cell lung cancer. **J Thorac Cardiovasc Surg** 109, 473-485.
- Urschel JD, Urschel DM, Anderson TM et al (1998) Prognostic implications of pulmonary satellite nodules, are the 1997 staging revisions appropriate? **Lung Cancer** 21, 83-87.
- US Department of Health & Human Services (1988) The health consequences of smoking, nicotine addiction, a report of the Surgeon General. **USHHS, CDC # 88-8406**.
- Veronesi G, Solli PG, Leo F, et al (2002) Low morbidity of bronchoplastic procedures after chemotherapy for lung cancer. **Lung Cancer** 36, 91-97.
- Weiden P, Piantadosi S (1991) Preoperative chemotherapy (cisplatin and fluorouracil) and radiation therapy in stage III non-small cell lung cancer, a phase II study of the Lung Cancer Study Group. **J Natl Cancer Inst** 83, 266-272.



H. Cuneyt Ulutin